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published in

Addiction
2004

DOI (link to publisher)

[10.1111/j.1360-0443.2004.00683.x](https://doi.org/10.1111/j.1360-0443.2004.00683.x)

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Smit, F., Bolier, L., & Cuijpers, W. J. M. J. (2004). Cannabis use and the risk of later schizophrenia: A review. *Addiction*, 99, 425-430. <https://doi.org/10.1111/j.1360-0443.2004.00683.x>

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Cannabis use and the risk of later schizophrenia: a review

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Submitted 14 July 2003;

initial review completed 2 October 2003;

final version accepted 5 December 2003

ABSTRACT

Aim To study the role of cannabis use in the onset of symptoms and disorders in the schizophrenia spectrum.

Design Review of five population-based, longitudinal studies on the relationship between cannabis use and problems ranging from the experience of psychotic symptoms to hospitalization with a confirmed diagnosis of schizophrenia. Several hypotheses are examined that may explain this relationship: (1) self-medication; (2) effects of other drugs; (3) confounding; (4) stronger effect in predisposed people, and (5) etiological hypothesis.

Findings Hypotheses 1 and 2 can be dismissed; hypothesis 3 is still open to debate, and converging evidence is found for hypotheses 4 and 5—antecedent cannabis use appears to act as a risk factor in the onset of schizophrenia, especially in vulnerable people, but also in people without prior history.

Conclusion There is an intrinsic message here for public health, but how that message is to be translated into action is not immediately clear.

KEYWORDS Cannabis, psychosis, public mental health, schizophrenia.

INTRODUCTION

It has been known for some time that there is a relationship between cannabis use and schizophrenia (Thornicroft 1990; Heeler, Dingemans & Linszen 1992). However, the precise nature of this relationship remained unclear: previous reviews were based mainly on cross-sectional or clinical studies. In these studies, the temporal sequence of cannabis use and schizophrenia could not be established, and it was difficult to disentangle effects of confounding, selection bias and the effects of other drugs (Degenhardt 2003). Consequently, the etiological status of cannabis use in the pathogenesis of schizophrenia remained the subject of a somewhat uninformed debate (Johns 2001; Hanak *et al.* 2002; Murray *et al.* 2003).

Recently, five large-scale longitudinal studies appeared in Sweden (Zammit *et al.* 2002), Israel (Weiser *et al.* 2002), New Zealand (two studies: Arseneault *et al.* 2002; Fergusson, Horwood & Swain-Campbell 2003) and the Netherlands (Van Os *et al.* 2002). These studies shed new light on the relationship between cannabis use and schizophrenia. Where insufficient proof used to

hamper a meaningful discussion about the etiological nature of the relationship, now converging evidence has emerged indicating that cannabis use does indeed act as a risk factor in the onset of schizophrenia.

It is worth noting that in this debate the term 'schizophrenia' is used as a catchword referring to a broad range of psychotic conditions. At one extreme it denotes the self-reported presence of psychotic symptoms (one study) and at the other extreme it means nothing less than hospitalization with a confirmed diagnosis of schizophrenia (two studies). Between these extremes are studies that have as outcomes the diagnoses of psychotic and schizophreniform disorder. Thus, the outcome that interests us here is better described as a continuum of psychotic symptoms and full-blown disorders in the schizophrenia spectrum. However, following common usage, 'schizophrenia' will be used as a generic name throughout this paper, unless more precise descriptions can be offered. We will return to this issue later.

Two other issues need also be mentioned here. This paper is restricted to the relationship between cannabis use and schizophrenia, but it should be noted that other

mental disorders, like depressive disorder, are the subject of a similar debate (Patton *et al.* 2002). Furthermore, we will not address the immediate psychotic reactions—such as hallucinations—that can be induced by heavy cannabis use. These are often seen as acute, toxic and usually transient reactions. In contrast to these immediate and temporary reactions, we will focus on the (often by several years) later onset of long-lasting schizophrenia. Therefore, the distinguishing features are the much greater time lag and the far more persistent, if not chronic, nature of the condition that will be discussed in this paper.

We will take the competing hypotheses that are customarily put forward to explain the relationship between cannabis use and schizophrenia as a starting point for this study. Next, we will describe how the recent studies tested the hypotheses. Finally, we will address the inferences that can be made and the implications they have for public mental health.

METHODS

Hypotheses

There are five hypotheses about the relationship between cannabis use and schizophrenia:

- 1 *The self-medication hypothesis.* Schizophrenia causes cannabis use because those already suffering from schizophrenia, or its symptoms, use cannabis in an attempt to cope with the negative symptoms (depressed or blunted affect) that stem from schizophrenia. People may also use cannabis in an attempt to suppress the side-effects of antipsychotic medication. The self-medication hypothesis thus implies a reversed causality.
- 2 *Other drugs hypothesis.* Cannabis use is often accompanied by the use of other drugs like amphetamines, opiates and cocaine, and it is not cannabis but the other drugs that are responsible for the later onset of schizophrenia.
- 3 *Confounding hypothesis.* Both cannabis use and schizophrenia are brought about by one or more common etiological factors. The relationship between cannabis use and schizophrenia thus is spurious.
- 4 *Interaction hypothesis.* Cannabis use may cause schizophrenia, but only in persons already at risk of becoming schizophrenic. In other words, these persons are in some way vulnerable (genetically or otherwise) and cannabis use only triggers the onset of schizophrenia.
- 5 *Etiological hypothesis.* Cannabis use makes its own (unique) contribution to the risk of becoming schizophrenic.

An etiological claim, such as in hypotheses 1, 4 and 5, can be made—within reasonable bounds—when the

following criteria are met (Rothman & Greenland 1998): (1) there is a probabilistic association between an *x*-variable (the assumed 'cause') and a *y*-variable (the 'effect'); (2) *x* precedes *y* in time, and (3) the influence of a confounder, *z*, that causes both *x* and *y* can be ruled out. An etiological claim can be further strengthened when a dose–response relationship can be found. Therefore, in people who used more cannabis, a proportionally greater risk of becoming schizophrenic must be observed. Later in this paper we describe how, in the new studies, attention was paid to the temporal sequence, confounding and dose–response.

Subjects, procedures and measures in the new studies

The Swedish study (Zammit *et al.* 2002) is a follow-up of a previously published historical cohort study of 50 087 military conscripts who were 18–20 years old in 1969–1970 (Andreasson *et al.* 1987). All conscripts received a medical examination and had to answer a questionnaire on drug use, including the use of cannabis. The conscripts were further examined by a psychologist and, if they presented symptoms of a mental disorder, also by a psychiatrist. At that time, 34 conscripts met the diagnostic criteria of the International Classification of Disorders (ICD) of a psychosis. They were excluded from the study. In the next step, 362 persons were identified who were hospitalized with an ICD diagnosis of schizophrenia or (paranoid) psychosis in the period 1970–1996 and of whom the military medical records could be traced. In this way, the relationship between previous cannabis use and later onset of schizophrenia could be established.

The study from Israel (Weiser *et al.* 2002) was conducted along similar lines. In the 1980s and 1990s, 50 413 conscripts who presented symptoms of behavioural or conduct disorders had to answer a questionnaire on drug use. Their medical records were later combined with data from the National Psychiatric Case Register. In all, 509 persons were identified who were hospitalized with a ICD-9 diagnosis of schizophrenia 4–15 years after their military service medical examination. For data analytical purposes, these cases were compared with 9215 former classmates who acted as 'healthy' controls.

The first study from New Zealand (Arseneault *et al.* 2002) was based on a birth cohort of 1037 people born in 1972–1973. When they had reached the age of 11, they were examined to see if they presented self-reported psychotic symptoms. At 15–18 years, the same procedure was followed to see if the subjects used cannabis. At the age of 26, they received a standardized diagnostic interview to see if they met the diagnostic criteria of schizophreniform disorder according the fourth version of the Diagnostic Statistical Manual (DSM-IV). At that

Table 1 Design, measures and outcomes of the reviewed studies.

Country	Study	Sample size	Design	Follow-up time	Definition of cannabis use	Definition of outcome	Effect size
Sweden	Zammit <i>et al.</i> (2002)	$n = 50,053$	Historical cohort study	11–14 years	Life-time cannabis use, frequency of use	Hospitalization with ICD-8/9 schizophrenia or paranoid psychosis	OR = 2.1–2.5 ^a
Israel	Weiser <i>et al.</i> (2002)	$n = 9,724$	Historical cohort study	4–15 years	Life-time cannabis use, ^b frequency of use	Hospitalization with ICD-9 schizophrenia	OR = 2.0
New Zealand	Arseneault <i>et al.</i> (2002)	$n = 1,253$	Birth cohort	15 years	Cannabis use ≥ 3 times	DSM-IV schizophreniform disorder	OR = 11.4 ^c
New Zealand	Fergusson <i>et al.</i> (2003)	$n = 1,011$	Birth cohort	3 years	CIDI/DSM cannabis dependency	Number of psychotic SCL-90 symptoms	IRR = 1.8
Netherlands	Van Os <i>et al.</i> (2002)	$n = 4,045$	Cohort study	3 years	Life-time cannabis use, frequency of use ^d	CIDI/DSM-III-R schizophrenia and other psychotic disorders ^e	OR = 3.5–3.7 ^f

^aDepending on the frequency of cannabis use: 11–50 times and >50 times; ^bmainly cannabis use; ^camong those who used cannabis before age 15; ^dless than once per month, 1–3 days per month, 1–2 days per week, 3–4 days per week, every day; ^econfirmed by a clinical re-examination using the Structured Clinical Interview (SCID), three items from the Brief Psychiatric Rating Scale (BPRS) and a consensus meeting attended by two psychologists and two psychiatrists using the Camberwell Assessment of Needs (CAN); ^fdepending on the pathology level in the outcome.

measurement, 96% of the birth cohort still participated in the study.

The second study from New Zealand (Fergusson *et al.* 2003) is another birth cohort with measurements on an annual basis until the cohort had reached the age of 16. Additional measures were taken at age 18. It was then ascertained whether the 1025 18-year-olds met the DSM-IV diagnostic criteria of cannabis dependency and whether psychotic symptoms were manifest. This was repeated at age 21, when 1011 people still participated in the study. Psychotic symptomatology was measured with the 10 psychosis items of the Symptom Checklist 90 (SCL-90). The corresponding scale had a reliability of 0.73 (Cronbach's α). When studying the relationship between cannabis use and schizophrenia, the researchers corrected for confounders (among them antecedent mental problems and social, family and personality characteristics).

The study that was conducted in the Netherlands (Van Os *et al.* 2002) was based on the data of the Netherlands Mental Health Survey and Incidence Study: NEMESIS (Bijl, Van Zessen & Ravelli 1998). This is a population-based cohort study among 7076 adults aged 18–65 years. Three measurement waves were carried out, in 1996, 1997 and 1999. In the last wave, 4848 people were retained. In the analyses, the possible effect of loss-to-follow-up was studied with the help of sensitivity analyses. DSM-III-R diagnoses (American Psychiatric

Association 1987) were ascertained in all three waves with the help of structured, computer-assisted, face-to-face interviews, using the Composite International Diagnostic Instrument (CIDI) (Smeets & Dingemans 1993). Respondents who scored positive on psychotic symptoms received a structured clinical re-examination by telephone. The results of both the CIDI interview and this re-examination were discussed systematically with two psychologists and two psychiatrists in order to reach consensus on the clinical status. The study was restricted to the 4045 people who had no prior history with symptoms of psychosis as established in the baseline measurement.

Table 1 lists characteristics of the studies and reports on their results. Table 2 lists how each of the studies dealt with the alternative hypotheses.

RESULTS

Which hypotheses can now be eliminated?

The self-medication hypothesis can probably be eliminated as a valid explanation for the relationship between cannabis use and the onset of schizophrenia. The studies under consideration employed several strategies to test the self-medication hypothesis. All studies looked into the temporal sequence and were interested to see what came first: cannabis use followed by schizophrenia, or the other

Table 2 Elimination of the alternative hypotheses in the reviewed studies.

Study	Eliminated effect of prior history of psychosis?	Eliminated the effect of other substances?	Eliminated the effect of confounders?	Studied interaction effect?	Found support for a dose-response relationship?
Zammit et al. (2002)	Yes, found temporal sequence and conducted analysis in psychosis-free group	Yes	Yes: IQ, social network, urbanicity	Not studied	Yes, larger risk of more cannabis use
Weiser et al. (2002)	Yes, found temporal sequence and conducted analysis in psychosis-free group	No	Yes, but confounders were not described	Not studied	Not studied
Arseneault et al. (2002)	Yes, found temporal sequence and adjusted statistically for history	Yes	No	Not studied	Not studied
Fergusson et al. (2003)	Yes, found temporal sequence and adjusted statistically for history	Yes	Yes ^a	Not studied	Not studied
Van Os et al. (2002)	Yes, found temporal sequence and conducted analysis in psychosis-free group	Yes	Yes: gender, age, ethnic descent, marital status, education, employment, urbanicity, experiences with discrimination	Yes, and this implies an etiological role of cannabis use	Yes, larger risk of more cannabis use

^aConfounders in the study of Fergusson et al. (2003): family (age of parents, educational level of parents, SES of parents); familial functioning (divorce, parental conflicts, life events, parental bonding, child abuse); parental adjustment (mental health, problem drinking, crime, illicit drug use); child (gender, neuroticism, sensation-seeking, IQ, educational attainment); medical history until age 16 (substance use and misuse and mental disorders, including anxiety and mood disorders).

way round. Some studies employed the strategy to conduct analysis on the subgroup that had no prior history of schizophrenia or symptoms thereof. Table 2 shows which strategy was followed for each study. For example, in the Swedish study 34 conscripts were excluded from the study because they showed signs of a psychotic disorder at the time of recruitment. In addition, a subgroup analysis was conducted in the group that developed schizophrenia only 5 years after conscription. In this way, subjects were excluded who might have used cannabis because they suffered from (prodromal symptoms of) schizophrenia. The study from the Netherlands was conducted exclusively on the 4045 people who had no history—on a lifetime basis—of psychotic symptoms. The same strategy was followed in the study from Israel, while both studies from New Zealand used statistical techniques to control for any prior history with symptoms of any mental disorder. In all these analyses, the results indicated that the later onset of symptoms and disorders in the schizophrenia spectrum was preceded by prior use of cannabis. This finding does not imply that people suffering from schizophrenia do not use cannabis as some form of 'self-medication', but these results do imply that cannabis use increases the risk of later schizophrenia even when self-medication can be ruled out as an explanation.

The other drugs hypothesis can be eliminated. It is true that cannabis users often use other drugs (Smit, Monshouwer & Verdurmen 2002), but multivariate analysis, in which the effects of other drugs are also evaluated, indicates that it is not the other drugs, but only cannabis that makes its own (unique) contribution to the risk of becoming schizophrenic. All studies, with the exception of the one from Israel, controlled for the influence of other substances. After controlling, the effect of cannabis use remained.

Which hypotheses are still uncertain?

The confounding hypothesis still leaves room for further debate. Both the Swedish and the Dutch study try, as far as possible, to control for confounding. The strength of the relationship between cannabis use and schizophrenia [expressed in odds ratios, (ORs)] becomes less and less when adjusted for more confounders. In the Swedish study, the ORs decrease by 30% after correction; in the Dutch study, ORs decrease by 20%. It is of note that in both studies the corrections were carried out for different sets of confounders, suggesting that the ORs will be reduced to half their original, unadjusted, values when corrected for all confounders—not to mention unob-

served confounders. The largest number of confounders were accounted for in the second study from New Zealand (see Table 2). After controlling, the effect [expressed in an incidence rate ratio (IRR), comparable with the OR] equals 1.8, while the unadjusted IRR was 2.3.

Which hypotheses find support?

The interaction hypothesis has now received a better empirical basis in the Dutch study. This study shows that vulnerable people (with a history of psychosis) have a much greater risk of schizophrenia than cannabis users without a history. The risk difference (RD) of using or not using cannabis is 2.2% for those without a history of psychosis, whereas RD = 54.7% in those with a history, and the underlying interaction effect was significant at $P < 0.001$ (Van Os *et al.* 2002). It is worth noting that the interaction hypothesis implies an etiological role of cannabis use in the onset of schizophrenia.

Finally, the etiological hypothesis has become more plausible through: (1) the elimination of the self-medication hypothesis; (2) the elimination of the other drugs hypothesis, and (3) support for the dose-response relationship, in which those who used more cannabis in the past will incur a proportionally greater risk of experiencing the later onset of schizophrenia, as has become clear in the Swedish and Dutch studies. In the Swedish study, it was shown that for people who used cannabis fewer than 50 times, the risk of becoming schizophrenic doubled, but for those using cannabis more frequently the OR was between 2.1 and 21.7, after adjusting for confounders (Zammit *et al.* 2002). A similar dose-response effect is reported in the Dutch study (Van Os *et al.* 2002).

DISCUSSION

This review aimed to answer the question of whether cannabis use increases the risk to develop symptoms and disorders in the schizophrenia spectrum. The results may now be summarized as follows. Five recent, longitudinal and carefully executed studies offer converging evidence that cannabis use does indeed increase the risk of schizophrenia and other psychotic disorders. This conclusion applies throughout the range of symptoms and full-blown disorders in the schizophrenia spectrum.

It is of note that alternative explanations (self-medication, use of other substances, effect of confounders) could be eliminated for the better part. This leaves ample room for the two remaining hypotheses: (1) cannabis use increases the risk but particularly in vulnerable people, and (2) cannabis use makes its own unique contribution to the risk of becoming schizophrenic. Both hypotheses find support, and both hypotheses imply an

etiological role of cannabis use in the pathogenesis of schizophrenia.

Some caution is required here. Epidemiological cohort studies do not lend themselves very well to proof that cannabis use will increase, in an etiological way, the risk of becoming schizophrenic. After all, the etiological claim can always be challenged by (unobserved) confounders, and it is too early to dismiss the confounding hypothesis. Furthermore, it is difficult to obtain accurate assessments of cannabis consumption and therefore the dose-response concept is also somewhat problematic. A plausible etiological theory, preferably underpinned by biomedical research on the effects of cannabinoids on the neurotransmitter systems, would be helpful here.

How large is the risk? With five new cases per 10 000 person years, the incidence rate of schizophrenia is small (Bijl *et al.* 2002). Assuming a causal mechanism, this risk will become larger—roughly by a factor 2—in cannabis users (see Table 1). The risk rate will then still be small, but its clinical consequences are to be taken seriously.

What can be said about the exposure to the risk? In the member states of the European Union and in the USA, 17.6% of 16-year-olds have used cannabis (Hibell *et al.* 2000). Thus even in this young age group the exposure rate is substantial.

The interaction hypothesis implies that vulnerable cannabis users have a much higher risk of becoming schizophrenic than others who are not vulnerable, but when would we describe a person as being vulnerable? There is little doubt about someone's vulnerability where there is a history of psychosis (Van Os *et al.* 2002), but this is obviously a small group and few people will regard themselves as vulnerable in this sense. However, the psychotic phenotype does not only express itself in its most extreme form—schizophrenia—but can also manifest itself in a single psychotic symptom. This is a fairly common experience with a prevalence of 17.5% in the general population (Van Os *et al.* 2000). The concept of vulnerability can have an even broader definition. On an annual basis, almost a quarter of the general population meets the diagnostic criteria of one or another DSM axis-I diagnosis (Bijl, Ravelli & Van Zessen 1998), and this tells us something about the distribution of vulnerability in the population. Thus, vulnerability can be defined in a more narrow or a more broad way, but it should be noted that the broader definitions have not been tested in the reviewed studies. The debate on cannabis use and later schizophrenia could therefore benefit from studies in which dose-response effects are studied across a broad range of vulnerability levels.

All in all, we conclude that the reviewed studies are the bearers of a message that contains six key elements: 1 Cannabis use roughly doubles the risk of becoming schizophrenic.

- 2 Many young people expose themselves to this risk.
- 3 The risk gets larger when more cannabis is used.
- 4 The risk also becomes larger in 'vulnerable' people.
- 5 Vulnerability may be a widespread, but difficult to recognize characteristic.
- 6 Even when the risk is numerically small, in clinical terms it is serious.

This is the message. However, it will require wisdom to formulate a health educational message that will generate a desirable effect. Warnings may not help and may even be counter-productive, but ignoring the message of the five studies is not an option.

ACKNOWLEDGEMENTS

This paper was previously published in *The Netherlands Journal of Medicine* [Nederlands Tijdschrift voor Geneeskunde (NTvG)]. The authors are grateful for the kind permission of the editorial board of NTvG to let us use the original article for this reworked version.

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